

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
OF THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Application of:
Minxue Zheng et al.

Confirmation No. 9085

Application Serial No. 10/667,191

Group Art Unit: 1637

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Examiner: Heather Calamita

Title: DUAL-PURPOSE PRIMERS AND PROBES FOR PROVIDING ENHANCED
HYBRIDIZATION ASSAYS BY DISRUPTION OF SECONDARY STRUCTURE
FORMATION

APPEAL BRIEF

Mail Stop Appeal

Commissioner for Patents
P.O. Box 1450
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Sir:

Applicants respectfully appeal the rejections set forth in the final Office Action for the above-referenced matter, which was e-mailed from the USPTO on November 9, 2010. As the claims under consideration have been twice rejected, the filing of this appeal is proper.

The Notice of Appeal for this matter was filed on February 10, 2011, with the appropriate fees. This Appeal Brief is timely filed within two months of the Notice of Appeal. Accompanying this paper is the fee specified in 37 C.F.R. § 41.20(b)(2) for the filing of this Appeal Brief. This paper is also accompanied by an Amendment under 37 C.F.R. §§ 1.116(b)(2) and 41.33.

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I. REAL PARTY IN INTEREST

The real party in interest is Siemens Healthcare Diagnostics, Inc., the assignee of record. The assignment documents showing the chain of title from the inventors to Siemens Healthcare Diagnostics, Inc. are recorded with the USPTO at Reel/Frame Nos. 014358/0220; 019769/0510; and 020333/0976.

II. RELATED APPEALS AND INTERFERENCES

The rejection of pending claims 1-18 and 26-35 in the subject patent application were previously appealed on March 27, 2008. On February 23, 2010, the Board of Patent Appeals and Interferences (“BPAP”) issued a Decision reversing the Examiner on all counts. There are no related interferences for this case.

III. STATUS OF THE CLAIMS

Claims 1-39 are pending. The Examiner has withdrawn claims 19-25 and 35-39 as drawn to a non-elected invention. Claims 1-18 and 26-34 were rejected in the final Office Action of November 9, 2010 (hereinafter the “FOA”), and are under appeal.

The same claims that are currently under appeal were previously appealed and upheld in the Decision of Appeal of February 23, 2010 (hereinafter the “Decision on Appeal”). The claims have not undergone any amendments since the Decision on Appeal and thus, this is the second appeal for pending claims 1-18 and 26-34.

With regard to the rejection of the pending claims, applicants take this opportunity to respectfully note that the Examiner’s statement on page 2 of the non-final Office Action of May 25, 2010 (hereinafter “NFOA”), that the additional art that was the subject of the NFOA, and that is the subject of the subject FOA, was not discovered until after the Decision on Appeal is not a true statement. The additional cited by the Examiner in both the NFOA and the FOA includes the Hogan et al. and the Honeyman et al. references. The Hogan et al. reference is cited in the Background of the instant application and was the first cited reference in the Information Disclosure Statement (hereinafter “IDS”) filed with the application papers on September 15, 2003 (reference AA). The Honeyman et al. reference was submitted in the IDS filed on August 2, 2004 (reference BI). Both the Hogan et al. and the Honeyman et al. references were acknowledged by the Examiner as considered in the attachments to the Office Action of August

9, 2006. Attached to this paper as Exhibit A is a copy of the signed PTO-1449 form for the Hogan et al. reference and attached to this paper is Exhibit B is a copy of the signed PTO-1449 for the Honeyman et al. reference. Both of the PTO-1449s show that the Examiner considered the references on July 27, 2006, a date well before the February 23, 2010, date of the Decision on Appeal.

Because the claims did not undergo any changes in claim scope since the submission of the Hogan et al. and Honeyman et al. references, it follows that the Examiner had the opportunity to apply the Hogan et al. and the Honeyman et al. references since at least as far back as the first Office Action on the merits. In this respect, applicants respectfully submit that the rejection of the claims over Hogan et al. and Honeyman et al. in the FOA is not in keeping with the USPTO's policy on compact prosecution.

IV. STATUS OF AMENDMENTS

An Amendment under 37 C.F.R. §§ 1.116(b)(2) and 41.33 was filed on March 29, 2011, in order to change the claim term "probe sequence" in claim 13 to --primer sequence--. Claim 1, from which claim 13 ultimately depends, recites a primer sequence, rather than a probe sequence; therefore, the change to claim 1 is supported by the claims. Additional support is found in the specification at *inter alia*, paragraph 0058. The amendment to claim 13 introduces no new issues into the application and serves only to place claim 13 in better form for appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 1-18 and 26-34 have two independent claims: claims 1 and 32.

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

As recited in claim 32, the present invention is directed to a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

Paragraphs 0003 and 0004 of the specification discuss how intermolecular secondary structures may block hybrid formation between an oligonucleotide and its target complementary sequence (page 2, lines 5-13). Paragraph 0005 provides an example of how secondary structure formation inhibits the identification of the SNP in each of the four exons of the cytochrome P450 CYP2D6 gene (page 2, lines 14-27). Paragraph 0006 explains that at the time of the invention, helper oligonucleotides (described in U.S. Patent No. 5,030,557 to Hogan et al.) were used to overcome the problem of the identification of target sequences within a secondary structure forming region. The Hogan et al. helper oligonucleotide method requires the addition of a molar excess (about 5 to 100 times that of the probe) of helper oligonucleotides to the nucleic acid probe sequence to assist the probe sequence to hybridize to the target sequence; the helper oligonucleotides of Hogan et al. must be longer than about 20 to about 50 nucleotides in length in order to be effective in blocking the formation of secondary structures (page 2, line 28, to page 3, line 4). Paragraph 0007 notes that disadvantages with the Hogan et al. method include the large excess of helper oligonucleotides over probe oligonucleotides that are required to implement the method as well as the long length of the helper oligonucleotides (page 3, lines 5-9).

As explained at paragraph 0008 of the specification, the dual-purpose primers of the present invention overcome the problem in the art of detection of a target sequence within a secondary structure forming region and improve upon the method of Hogan et al. by providing a dual-purpose primer that is capable of identifying a target sequence within a secondary structure forming region with a *single* oligonucleotide comprised of a blocking sequence that can be substantially shorter than the Hogan et al. helper oligonucleotides and which also does not have to

have perfect complementarity with the secondary structure forming region of the target molecule (page 3, lines 18-23).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 1-5, 9-14, 26, and 32 are anticipated under 35 U.S.C. § 102(b) by Honeyman et al.
2. Whether claims 6-8, 15, and 16 are obvious under 35 U.S.C. § 103(a) over Honeyman et al. in view of Laibinis et al. (U.S. Pub. No. 2002/0028455).
3. Whether claims 10 and 11 are obvious under 35 U.S.C. § 103(a) over Honeyman et al. in view of Switzer et al. (Biochemistry, 1993).
4. Whether claims 17, 18, 33, and 34 are obvious under 35 U.S.C. § 103(a) over Honeyman et al. in view of Beattie et al. (U.S. Pat. No. 6,268,147).
5. Whether claims 27-31 are obvious under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of the Stratagene Catalogue (1988).
6. Whether claims 1 and 32 are anticipated under 35 U.S.C. § 102(b) Hogan et al. (USPN 5,030,557).

VII. ARGUMENT

A. CLAIMS 1-5, 9-14, 26, AND 32 ARE NOT ANTICIPATED BY HONEYMAN ET AL.

Applicants appeal the rejection of claims 1-5, 9-14, 26, and 32 as anticipated under 35 U.S.C. § 102(b) by Honeyman et al. For purposes of the appeal of this rejection, claims 1-3, 26, and 32 stand together; claim 4 stands alone; claims 5, 9, and 12 stand together; and claims 13 and 14 stand together.

It is well-established that a *prima facie* case of anticipation requires that every element of a patent claim must be found, either expressly or inherently, in a single prior art reference. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed. Cir. 1992).

The following discussion will show why the Honeyman et al. reference does not anticipate the claimed invention.

1. THE TEACHINGS OF HONEYMAN ET AL.

Honeyman et al. teach a snapback method of single-stranded conformation polymorphism (SSCP) analysis for genotyping Golden Retrievers for the X-linked muscular dystrophy allele (Abstract). At column 1 of page 734, Honeyman et al. explain that the causative mutation of the X-linked form of muscular dystrophy in Golden Retrievers is a single base change within the 3' splice site of intron 6 in the canine dystrophin gene. The mutation results in a loss of exon 7 and disruption of the reading frame so that transcription of the dystrophin gene is prematurely truncated by an in-frame stop codon in exon 8.

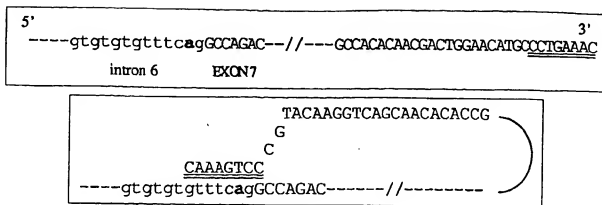
As explained by Honeyman et al. at column 2 of page 734, the truncation of the dystrophin gene results in difficulties in genotyping the dogs. While two PCR procedures can be used to overcome the genotyping difficulties, Honeyman et al. acknowledge that using two PCR procedures is time consuming and cumbersome. As an alternative to the two PCR approach, Honeyman et al. suggest the use of an SSCP analysis, which Honeyman et al. explain is a quick, simple method of detecting genetic mutations. The method involves diluting and heat denaturing PCR products in formamide loading buffer and fractionating the material on a polyacrylamide gel under nondenaturing conditions; no manipulation of the PCR product besides gel fractionation is required. Honeyman et al. note that one limitation of SSCP analysis is that many base changes, up to 30%, may be missed.

To overcome the limitation in the SSCP analysis, Honeyman et al. developed a snapback method of SSCP analysis where a snapback primer is designed using one of the original primers to which an additional sequence that is complementary to the normal sequence flanking the mutation under investigation is added to the 5' terminus. The snapback primer replaces the original forward or reverse primer used in the PCR procedure, with the result that PCR products of the snapback primer will have a terminus with the potential of reannealing or snapping back to the normal allele, but not to the mutant allele. As a result of the snapback, *the PCR products of the normal dogs will have secondary or tertiary structure conformation changes, while the PCR products of the mutant dogs will not.* As explained in column one of page 736 and as shown in Figure 2 of Honeyman et al., because of the conformational secondary or tertiary structure change in the snapback SSCP PCR product, *the snapback SSCP PCR product migrates at a different rate than the conventional SSCP PCR product.* As show in Figure 2, the PCR product for the unaffected (N), carrier (C), and affected dogs (A) migrated at different rates with the

snapback SSCP primers, but not with the conventional SSCP primers (*see also*, para. bridging pp. 735-736 and page 736, col. 1, 1st full para.). As also noted on column one of page 736 (1st full para., last line), *the nucleotide mismatch in the mutant allele prevented the snapback, which resulted in a faster migration of the PCR product of the mutant allele on the fractionated gel* (Figure 2).

At column two of page 736, Honeyman et al. teach that the use of a primer at a distance as great as possible (*e.g.*, at least 70 bases) from the normal sequence flanking the mutation site was optimal because the arrangement generated the most substantial single-strand conformation change. Honeyman et al. explain that snapback primers that were designed to anneal only a few bases away from the normal sequence flanking the mutation were successful for detecting the mutant allele, but not the normal product.

The method of Honeyman et al. is illustrated in Figure 3 (reproduced below), which shows the nucleotide sequences involved in the snapback genotyping analysis of Golden Retriever puppies from a colony of dogs with X-linked muscular dystrophy. The top portion of Figure 3 shows a portion of the sequence for the normal allele of the canine dystrophin gene. In dogs with muscular dystrophy, an adenine residue (shown in bold in the figure) in the 3' splice site of intron 6 (shown in lower case letters) is replaced by a guanosine residue. Also shown in Figure 3 is the priming site for the GR1-SB snapback primer (the last 8 nucleotides shown in underlined upper case letters). The bottom portion of Figure 3 shows the last 8 nucleotides snapping back and priming to the forward single strand of the amplified normal allele. Figure 3 clearly shows that the snapback process of Honeyman et al. involves a single stranded DNA with a snapback primer annealed some distance from the site of interest (*i.e.*, the SNP at intron 6 of exon 7), wherein the snapback primer primes to the site of interest to form a loop (*i.e.*, a secondary structure).



2. THE CLAIMED INVENTION IS NOT LIKE HONEYMAN ET AL.

Applicants have explained in prior Office Action responses, including the Appeal Brief filed on July 9, 2008, which addressed the prior rejection of the claims over *inter alia*, Wilton et al., that the claimed invention is *not* directed to a procedure by which a site of interest becomes part of a secondary structure formed in a single-stranded nucleic acid sequence, rather, the claimed invention is directed to primers and probes that *disrupt* secondary structures that conceal an SNP site. Both Wilton et al. and Honeyman et al. describe primers that are designed to *introduce* a secondary structure into a gene in order to view a mutation on a gel by comparing the migration rate of the normal gene versus the mutant gene. By contrast, the purpose of the claimed primers and probes is to expose a site of interest that is otherwise not capable of detection or amplification by way of hybridization because the site of interest site is located proximal to or within a secondary or tertiary structure and is therefore inaccessible. In this regard, it is axiomatic that the primers and probes of the claimed invention are designed to achieve the opposite result of the primers and probes of both the Wilton et al. and the Honeyman et al. references. Figures 5 and 10 of the instant application illustrate how the primers of the claimed invention work (reproduced below).

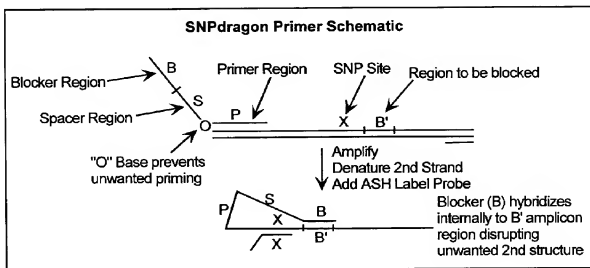


FIG. 5

As explained in paragraphs 0019 and 0057 of the specification of the instant application, Figure 5 schematically illustrates the structure and mechanism of action of the dual-purpose primer of the claimed invention. The primer sequence is complementary to one terminus of the target molecule that contains the SNP site (X) and the blocking sequence is substantially complementary to a sequence B' immediately adjacent to X, wherein B' is the segment of the target molecule responsible for generating an intramolecular secondary structure that, in the absence of the claimed dual purpose primer, would conceal the SNP site from a complementary sequence (thereby preventing hybridization and detection). After amplification of the target nucleotide sequence and reannealing, B hybridizes with B' in the amplicon, blocking formation of the unwanted secondary structure and allowing the SNP site (X) to be detected and amplified.

A comparison of Figures 3 of Honeyman et al. and Figure 5 of the instant application reveals the differences between the snapback primer of Honeyman et al. and the primers and probes of the claimed invention. In Honeyman et al., the SNP site is within the linear single stranded DNA and the 3' terminal 8 nucleotides of the GR1-SB primer *snaps back and hybridizes directly to the SNP site of the normal allele*. The identification of the Honeyman et al. SNP site occurs by tracking the faster migration of the oligonucleotides obtained from the mutant allele (with no secondary structure) versus the slower migration of the oligonucleotides obtained

from the non-mutant allele (with the secondary structure). By contrast, with the claimed invention, the SNP site is hidden by a secondary structure site (B') and the blocking sequence binds to the secondary structure site (B') thus disrupting it and exposing the SNP site for amplification. Figure 10 further illustrates this feature of the claimed invention.

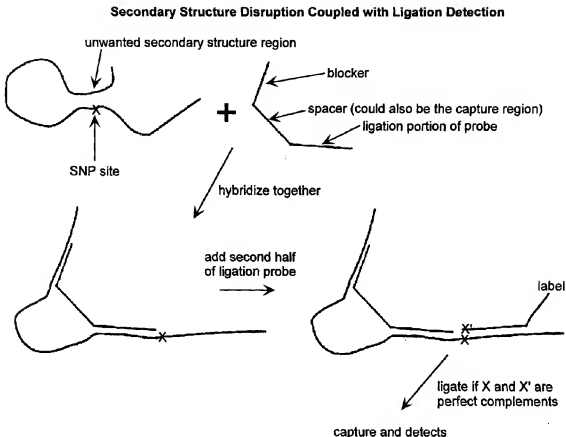


FIG. 10

3. CLAIMS 1-3, 26, AND 32

Claims 1 and 32 are reproduced above under the Summary of the Claimed Subject Matter. Claim 2 depends from claim 1 and recites that the site of interest of claim 1 is a nucleic acid sequence. Claim 3 depends from claim 2 and recites that the site of interest of claim 2 is an SNP. Claim 26 depends from claim 1 and is directed to an amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence.

In the rejection of claims 1 and 32 (FOA, pp. 2-3), the Examiner takes the position that Honeyman et al. teach a primer that has a priming sequence and a blocking sequence identical to (a) and (b) of the primers and probes of independent claims 1 and 32. The Examiner reproduces the allegedly anticipatory Honeyman et al. primer on page 4 of the FOA (under the rejection of claim 26); there, the Examiner highlights the portion of the GF2 sequence that she believes reads on the primer sequence (a) of the claimed invention with underlining and the portion that she believes reads on the blocking sequence (b) of the claimed invention with italics. The sequence as highlighted by the Examiner on page 4 of the FOA is reproduced below:

5'-CTT AAG GAA TGA TGG GCA TGG G-3'

Applicants note that the Honeyman et al. primer reproduced above is the GF2 primer sequence set forth on page 735 of Honeyman et al. (col. 1, Materials and Methods).

On page 735 of Honeyman et al., it is taught that for the *conventional* SSCP analysis, primers GF2 (forward primer) and GR1 (reverse primer) were used. Honeyman et al. teach that the GF2 primer corresponds to basepairs 135 through 114 of the canine dystrophin gene on intron 6 and that the GR1 primer corresponds to basepairs 805 through 782 of exon 7. The GF2 and GR1 primers of Honeyman et al. have the following sequences.

GF2 (intron 6): 5'-CTT AAG GAA TGA TGG GCA TGG G-3'

GR1 (exon 7): 5'-TGC ATG TTC CAG TCG TTG TGT GGC-3'

For the *snapback* SSCP analysis, primer GR1 and a snapback primer GR1-SB were used. Honeyman et al. teach that the GR1-SB snapback primer was designed by replacing the 5' terminal thymine of the GR1 primer (highlighted in the GR1 primer above with underlining) with a GTTTCAGG sequence (highlighted in the GR1-SB primer below with underlining). The GR1-SB snapback primer has the following sequence.

GR1-SB: 5'-GTTTCAGGGC ATG TTC CAG TCG TTG TGT GGC-3'

Figure 3 of Honeyman et al. shows how the complement to the GR1-SB snapback primer (3'-CAAAGTCC) hybridizes to the complementary target sequence on intron 6 (5'-gtttcagg) thus forming the snapback loop, which has already been discussed in detail above.

The foregoing discussion explains that Honeyman et al. used the GF2 and the GR1 primers for conventional SSCP analysis and the GR1-SB primer for the snapback analysis. As noted above, the Examiner is taking the position that the Honeyman et al. GF2 primer anticipates

the primers and probes of independent claims 1 and 32. The following discussion will explain why this is not the case.

With regard to the actual teachings of Honeyman et al., applicants submit that the reference does not teach or suggest that the GF2 primer is useful for detecting a site of interest; rather, in fact, it teaches that the GF2 primer is *not* useful for such a purpose. In the first paragraph of the Discussion (p. 736, col. 1), Honeyman et al. explain that the conventional SSCP primers were not useful in identifying the X-linked Dystrophin disease state in tested dogs. As discussed above under the Discussion of the Teachings of Honeyman et al. and as shown in Figure 3 of Honeyman et al., the X-linked Dystrophin disease state was identified by using primers that identify the adenosine to guanine replacement site in the sequence 5'-GTTTCAGG-3' at the 3' splice site of intron 6. Since the GF2 primer of Honeyman et al. was used for the unsuccessful conventional SSCP analysis, it follows that the GF2 primer identified by the Examiner is not a primer that one of ordinary skill in the art would pull from Honeyman et al. to arrive at the claimed primers and probes, which are designed to identify a site of interest for a disease state.

With regard to the Honeyman et al. site of interest, in the rejection of claim 3 (FOA, p. 3), the Examiner correctly identifies the site of interest of the canine dystrophin gene disclosed in Honeyman et al. as the adenine-guanosine SNP replacement site in the sequence 5'-GTTTCAGG-3' on intron 6. As is shown above, this sequence is identical to the 5' terminal sequence that is added to the GR1 primer to form the GR1-SB primer. As is evident in Figure 3 of Honeyman et al., the site of interest is not shown to be within a secondary structure forming region, rather, the site of interest is shown clearly as being within a linear sequence in intron 6 of the canine dystrophin gene. As explained in detail above, the secondary structure shown in Honeyman et al. is the result of the snapping back of the GR1-SB primer to the site of interest in the normal allele, but not the mutant allele. In the mutant allele, the site of interest will have the sequence 5'-GTTTCGGG-3', which will not anneal to the GR1-SB snapback sequence (*i.e.*, 3'-CAAAGTCC-5'). Because upon amplification, the mutant allele of the canine dystrophin gene will not snapback forming a secondary structure, on a gel, the linear mutant allele will migrate faster than the secondary-structure containing normal allele.

Despite the Examiner's proper acknowledgement of the Honeyman et al. canine dystrophine gene SNP site of interest as 5'-GTTTCAGG-3', applicants note that this site of interest does *not* have a complement on the GF2 primer.

A proper reading of independent claims 1 and 32 requires that a target sequence, with a site of interest, be proximal to or within a secondary structure forming region and that the primers and probes of the claimed invention have a sequence (a) that corresponds to the site of interest and (b) a segment of the secondary structure forming region. Applicants submit that the Examiner has not shown this to be the case with the Honeyman et al. GF2 primer, which does not include the adenosine-guanosine replacement site on intron 6 of the canine dystrophin gene and is not involved in the disruption of secondary structures within either intron 6 or exon 7.

For the sake of argument and further explanation, applicants note that the GR1 primer, which was used to make the GR1-SB snapback primer corresponds to basepairs 805 to 782 of exon 7. Unlike the GF2 primer, the GR1-SB primer is shown in Figure 3; however, the GR1 primer is not shown to anneal to any part of intron 6 or exon 7. What Figure 3 does show is the 5' terminal end of the GR1-SB snapback primer annealing to the 5'-GTTTCAG-3' site of interest on intron 6.

With regard to the actual sequence of the GF2 primer, Honeyman et al. do *not* teach or suggest that the GF2 primer has a priming sequence equivalent to (a) or a blocking sequence equivalent to (b). In fact, the only teaching in Honeyman et al. regarding the GF2 primer is found in the third paragraph of col. 1 of page 735 (Materials and Methods) where the sequence of the primer is shown and where it is taught that the GF2 primer corresponds to basepairs 135 through 114 of intron 6 of the canine dystrophin gene. A review of the sequence of the GF2 primer versus the sequence of intron 6 in Figure 3 shows that the sequence of the GF2 sequence (intron 6 base pairs 135 to 114), or its complement, is not found anywhere in Figure 3. Indeed, Figure 3 only shows the sequence 5'-gtgtgt**gtttcag**-3' from intron 6 with the site of interest highlighted in bold and the mutation replacement site highlighted in bold italics; no information regarding the exact location of the site of interest on intron 6 is provided in Honeyman et al.

In the rejection of claim 26 (FOA, pp. 4-5) and in the Response to Arguments (FOA, pp. 9-10), the Examiner attempts to elucidate the how the GF2 primer reads on the primers and probes of claims 1 and 32. There, the Examiner reproduces the Honeyman et al. GF2 primer, which as previously noted is used for the conventional SSCP analysis, underlines the sequence

AAGGAAT as being equivalent to the primer sequence (a) of claims 1 and 32, italizes the sequence GATCC as being equivalent to the blocking sequence (b) of claims 1 and 32, and fabricates a target sequence, which the Examiner asserts would be disrupted when hybridized to the GF2 primer. There are many things wrong with this approach.

First, the Honeyman et al. site of interest (GTTTCAG) does not appear in the Examiner's "target" sequence set forth on page 4 of the FOA and, as noted above, the complement to the site of interest (CAAAGTC) does not appear anywhere in the GF2 primer; accordingly, the Examiner's primer:target complement does not appear to be based upon a recognition of the site of interest from Honeyman et al., which is acknowledged by the Examiner as being the adenosine-guanosine SNP replacement site. In this regard, applicants submit, that the Examiner's primer:target complement shown on page 4 of the FOA is *not* based upon the teachings of Honeyman et al., but rather, is based solely upon a primer:target complement of the Examiner's own making. Because the instant anticipation rejection is based solely upon the single Honeyman et al. reference, it is a statutory requirement that Honeyman et al. *must* teach, expressly or inherently, all of the claim limitations. 35 U.S.C. § 102; *Minn. Mining & Mfg.*, *supra*. In this regard, the Examiner's conclusion on page 5 of the FOA that the hybridization of the italicized portion of the GF2 primer on page 4 of the FOA would hybridize to the italicized portion of the "target" on page 4 of the FOA, thus disrupting the secondary structure formation of the target, has absolutely no basis whatsoever in the teachings of Honeyman et al. and should not be given any weight by this Honorable Board.

Second, nowhere in Honeyman et al. is it taught or suggested that the sequence underlined by the Examiner (AAGGAAT) is complementary to a segment of a target nucleotide sequence other than a secondary structure forming region or that the sequence italicized by the Examiner (GATCC) is blocking secondary structure formation. In the FOA, the Examiner attempts to correct these omissions from Honeyman et al. by stating that the teachings are inherent (FOA, p. 5, top para.), but this is *not* the case. Applicants submit that any reading into Honeyman et al. that the sequence AAGGAAT of the GF2 primer is complementary to a segment of the target nucleic acid other than a secondary structure forming region, and that the sequence GATCC of the GF2 primer is blocking secondary structure formation on the target nucleic acid, does not come from Honeyman et al., but rather, is based upon the disclosure of the instant application and as such, constitutes an impermissible hindsight reconstruction of the

claimed invention. *In re Deuel*, 51 F.3d 1551, 1558 (Fed. Cir. 1995) (It is well-established that an obviousness analysis that relies upon the applicant's disclosure rather than the prior art is improper as being based upon an impermissible hindsight reconstruction); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this regard, applicants submit that the Examiner's "inherency" argument is so far removed from the teachings of Honeyman et al., and so deeply entrenched in a hindsight reconstruction, that it appears that the Examiner could pull any primer sequence from any article in the entire universe of biotechnology publications, fabricate a target as was done on page 4 of the FOA, and claim that the primer "inherently" reads on the claimed invention.

Third, with respect to secondary structure formation, as noted above (under the discussion of the Teachings of Honeyman et al.), Honeyman et al. expressly teach that *the mutations that could not be detected using the conventional SSCP primers* (such as the forward GF2 primer referenced by the Examiner) *are those mutations that are not involved in the secondary or tertiary structure of the single stranded PCR product* (p.734, col. 2; p.736, col. 1). These express teachings combined with the additional express teaching from Honeyman et al. that *the GF2 primer was not able to distinguish mutant from normal or carrier dogs* (para. bridging pp. 735-736, col. 1; Fig. 2) leads to the inherent teaching that *the GF2 primer is priming to a site on the canine dystrophin gene that has no secondary or tertiary structure*. Indeed, this deficiency in the target gene is the precise reason that Honeyman et al. developed the snapback SSCP primer; specifically, *to introduce single stranded conformational changes to the PCR product* (Fig. 3) *so that the migration of the normal PCR product would be different from the migration of the mutant PCR product* (Fig. 2).

Fourth, in the paragraph bridging pages 9-10 of the FOA, the Examiner takes the position that the Honeyman et al. 5'-GTTTCAG-3' site of interest does not need to be shown in the target sequence set forth on page 4 of the FOA, and that the complementary priming sequence on the GF2 primer also does not need to be shown, because the site of interest and the complement are not claimed; rather, they are in the target, not the primer. Applicants submit that this line of reasoning turns the Examiner's own rejection on its head. On page 3 of the FOA, the Examiner specifically identifies the site of interest of Honeyman et al. as relevant to the use of the Honeyman et al. primer, yet when the Examiner has to provide a rationale for the Honeyman et

al. primer reading on the claimed primers and probes, the Examiner ignores the Honeyman et al. site of interest, fabricates a different “site of interest” that is not found in Honeyman et al., identifies a complementary sequence on the GF2 primer that is not taught in Honeyman et al., and argues that the site of interest and the GF2 complementary sequence are not relevant because they are not claimed. This line of reasoning is clearly not sound. Independent claims 1 and 32 very clearly recite that the claimed primers and probes bind to a site of interest; thus, it follows that the site of interest on the target determines the structure of the claimed primers and probes. In this regard, if the Examiner chooses to cite a particular reference for a site of interest, it follows that the reference should disclose a primer that is designed to detect and amplify the site of interest. To do so otherwise discredits the merits of the rejection.

Lastly, in order to obtain additional information regarding the Examiner’s identification of a target and primer site outside the teachings of Honeyman et al., in the response filed on August 23, 2010, applicants requested that the Examiner provide documentary evidence of the information pursuant to MPEP § 2144.03. The Examiner’s response to this request was that it was “inappropriate” (FOA, p. 10) and that all of the facts in the anticipation rejection are “provided directly in the prior art document(s)” and are “expressly stated within the reference(s).” As is clear from the discussion set forth herein, this is not the case. The mere fact that the site of interest on the target molecule on page 4 of the FOA is not found in Honeyman et al., and the corresponding priming and blocking sites on the GF2 primer are not identified in Honeyman et al., proves that the Examiner is using information that is beyond the scope of Honeyman et al. Further, the Examiner’s pronouncement on page 9 of the FOA that Honeyman et al. “expressly” teaches the target and primer is not consistent with the Examiner’s inherency arguments set forth at pages 3 and 4 of the FOA. Applicants submit that the inconsistencies in the FOA regarding the teachings of Honeyman et al. and the Examiner’s failure to provide necessary information in order to justify the rejection of independent claims 1 and 32 leads to a conclusion that the Examiner’s rejection of the claimed invention is not meritorious.

Applicants submit that none of the primers in Honeyman et al. are the same, either expressly or inherently, as the primers and probes of claims 1-3, 26, and 32 for at least the foregoing reasons.

4. CLAIM 4

Claim 4 depends from claim 1 and recites that the primer sequence of claim 1 is complementary to one terminus of the target molecule containing the target nucleotide sequence.

In the analysis of claim 4, the Examiner states that “Honeyman et al. teach the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence” and cites Figure 3 for support. Applicants submit that the Examiner is taking Figure 3 completely out of context. Figure 3 shows the complement of the 5' terminal site of the GR1-SB snapback primer folding over to hybridize to the site of interest on the normal canine dystrophin gene to form the secondary structure that will allow the genes to be viewed on a gel. As set forth in the discussion of claims 1-3 and 32, the Examiner is treating the GF2 primer (5'-CTT AAG GAA TGA TGG GCA TGG G-3') as equivalent to the primer of the claimed invention; however, as explained above, the GF2 primer is not shown in Figure 3. Further, as also explained above, Honeyman et al. teach that the conventional SSCP analysis was not capable of identifying the mutated canine dystrophin gene (Discussion, p. 735, col.1); therefore, it follows that the GF2 primer, which Honeyman et al. taught as used in the conventional SSCP analysis (Materials and Methods, p. 735, col. 1) was not successful in identifying the canine dystrophin gene mutation. In order to detect the canine dystrophin gene mutation, the GR1-SB snapback primer was needed.

Notwithstanding the foregoing, as noted repeatedly above, neither the non-mutated nor the mutated canine dystrophin gene is located within a secondary structure forming region; therefore, the comparison of Figure 3 with the claimed invention is completely inaccurate. In order for the claimed primer to work, the site of interest must be proximal to or within a secondary structure forming region. In the Honeyman et al. case, the site of interest is not within a secondary structure, it is exposed within a linear sequence, and therefore, there is no reason to have to disrupt the gene in order to detect and amplify the site of interest.

On this issue, applicants note two additional teachings from Honeyman et al. that further distance this reference from the claimed invention. In the paragraph bridging columns 1-2 of page 734, Honeyman et al. explain that the causative mutation in the canine dystrophin gene is a single base change within the 3' splice site of intron 6 (*i.e.*, the A to G replacement discussed herein). The change results in a loss of exon 7 and disruption of the reading frame so that transcription of the dystrophin gene is prematurely truncated by an in-frame stop reading codon.

In the second paragraph of the Discussion (p. 736, col. 1), Honeyman et al. explain that it has been suggested that base changes that cannot be detected by conventional SSCP analysis are those that are located in a region of a sequence that is not involved in the overall conformation of the PCR product. Based upon these teachings alone, one of ordinary skill in the art would appreciate that the failure of the conventional SSCP primer to identify the mutated gene is not anything that is proximal to or at the site of the mutation, but rather, as Honeyman et al. explain, it is something that is downstream from the site of mutation. These teachings from Honeyman et al. are inapposite to what the claimed invention is about, which is the disruption of a gene conformation, *i.e.*, a secondary structure, that obfuscates the site of interest.

Applicants submit that Figure 3 of Honeyman et al. does not read on claim 4 for at least the foregoing reasons.

5. CLAIMS 5, 9, AND 12

Claim 5 depends from claim 1 and recites that the primer of claim 1 further includes a nonhybridizing spacer between the primer sequence and the blocking sequence. Claim 9 depends from claim 5 and recites that the nonhybridizing spacer of claim 5 is nucleotidic. Claim 12 depends from claim 9 and recites that the nucleotidic nonhybridizing spacer of claim 9 is an oligomeric segment of a recurring single nucleotide.

In support of the rejection of claim 5, the Examiner cites Figure 3 and takes the position that the non-hybridizing sequence in Figure 3 is the sequence that anneals back to the normal sequence and therefore does not hybridize with the target sequence carrying the mutation.

Applicants submit that the Examiner's rationale for Figure 3 reading on claim 5 is not readily understandable. Claims 5, 9, and 12 are clearly directed to a non-spacer sequence that is between a priming sequence and a blocking sequence, the former of which hybridizes to a target sequence and the latter of which hybridizes to a portion of the secondary structure forming region of which the target is proximal to or located within. The way the Examiner's rejection of claim 5 is written, it appears to be directed to the sequence at the 3' terminal end of the GR1-SB snapback primer, *i.e.*, 5'-CCTGAAAC-3', which anneals to the site of interest of the normal canine dystrophin gene allele, *i.e.*, 5'-gtttcagc-3', but not to the mutated canine dystrophin gene, *i.e.*, 5'-gtttcgcc-3'. Applicants submit that the non-hybridizing spacer of claims 5, 9, and 12 is nothing like the 3' terminal end of the GR1-SB snapback primer. Indeed, it is unarguable that the 3' terminal end of the GR1-SB snapback primer is not a spacer; rather, it is clearly the

terminal end of the GB1-SB primer. To be sure, Honeyman et al. expressly teaches this to be the case (*see, e.g.*, Materials and Methods, p. 735, col. 1, para. 3, last two sentences).

Assuming *arguendo* that the Examiner meant to identify the non-annealing part of the GB1-SB snapback primer as equivalent to the non-hybridizing spacer of claims 5, 9, and 12, applicants submit that this part of the snapback primer is also nothing like the non-hybridizing spacer of claims 5, 9, and 12. In this regard, applicants direct this Honorable Board to Figures 5 and 10 of the instant application, which should be viewed together in order to appreciate the claimed invention schematically. In both figures, the spacer region is shown between the blocker region and the primer region. In Figure 10, the SNP site is shown within the secondary structure forming region. The combination of the hybridization of the blocker sequence and the priming sequence disrupts the secondary structure, thus exposing the SNP site for detection. The spacer is inserted into the primer to ensure sufficient disruption of the secondary structure. Figure 3 of Honeyman et al. does not show such a configuration.

As discussed in Honeyman et al. (p. 736, Discussion, cols. 1-2), the GR1-SB snapback primer was placed at as great a distance as possible from the normal sequence flanking the mutation because this allowed for the generation of the most substantial conformation change; thus, it follows that in Honeyman et al., the non-hybridizing sequence of the GR1-SB snapback primer is located at a substantial distance between the normal gene site of interest and the priming site of the GR1-SB snapback primer. Applicants submit that there is no blocking sequence shown in the sequence of the GR1-SB snapback primer of Figure 3. Indeed, under Honeyman et al., there is nothing to block since the purpose of Honeyman et al. is to prime in such a way that a secondary structure is formed at the 3' end of intron 6.

As is evident from this discussion, the Examiner is citing the GF2 primer where it is convenient and the GR1-SB primer where it is convenient without appearing to appreciate that these two primers are in fact quite different, with the GF2 primer used to run the conventional SSCP analysis as a control experiment and the GR1-SB primer being used to run the snapback SSCP analysis.

With regard to claims 9 and 12, the Examiner cites the Materials and Methods section of Honeyman et al. (p. 735, col. 1) as supporting a nucleotidic spacer (claim 9) that may be comprised of an oligomeric segment of a recurring single nucleotide (claim 12). A review of the

Materials and Methods section of Honeyman et al. shows absolutely no mention of preparing a spacer within the convention GF1 and GR2 primers or the snapback GR1 and GR1-SB primers.

Applicants submit that Figure 3 and the Materials and Methods section of Honeyman et al. does not read on claims 5, 9, and 12 for at least the foregoing reasons.

6. CLAIMS 13 AND 14

Claim 13 depends from claim 1 and recites that the probe sequence and the spacer sequence are separated from each other by means for halting transcription therebetween. Claim 14 depends from claim 13 and recites that the means for halting transcription is an arresting linker.

On page 4 of the FOA, the Examiner takes the position that the separation of the primer sequence from the snapback sequence of Honeyman et al. satisfies the structural limitations of claims 13 and 14 and adds that because the means for halting transcription and the arresting linker limitations of claims 13 and 14 are functional, the limitations are inherently met by the primer of Honeyman et al. The approach taken by the Examiner with respect to claims 13 and 14 is not appropriate and should be given no weight by this Honorable Board.

It is well-established that “means-plus-function claiming applies only to purely functional limitations that do not provide the structure that performs the recited function.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1311 (Fed. Cir. 2005). In the instant case, claim 13 is a means-plus-function claim, but claim 14 is not since it recites a specific structure, *i.e.*, an arresting linker. With regard to claim 13, just because the language in that claim is in means-plus-function format does not mean that the Examiner is exempt from locating a reference that teaches the claim limitation. In this case, the Examiner makes no effort to find a reference that teaches means for halting transcription or an arresting linker and instead argues that such teachings are inherent within the Honeyman et al. primer. A review of Honeyman et al. shows that there is absolutely no teaching or suggestion therein regarding a means for halting transcription, such as an arresting linker and arguing that such elements are inherent in the primer of Honeyman et al. is insufficient grounds for a rejection of these two claims over Honeyman et al.

Applicants submit that the Honeyman et al. primer does not inherently read on claims 13 and 14 for at least the foregoing reasons.

7. THE EXAMINER CONTINUES TO IGNORE THE CLAIM LIMITATIONS

Prior to the Decision on Appeal (attached to this paper), applicants spent two years (from Nov. 8, 2006 to Dec. 5, 2008) arguing that the Wilton et al. reference did not read on the claimed invention because Wilton et al. taught a snapback SSCP primer that forms secondary and tertiary structures in order to visualize the gene being detected on a gel. The Examiner's rationale for citing Wilton et al. as reading upon the claimed invention was that the blocking sequence (b) of the claimed primers and probes was a functional limitation that was not entitled to any patentable weight. In the Decision on Appeal, the BPAI reversed the Examiner on all counts and in so doing informed the Examiner that all claim limitations, whether recited structurally or functionally, must be considered.

Upon the return of the case to the Examining Corps, the Examiner issued new rejections citing Honeyman et al. and Hogan et al. as the primary references. As is evident from the discussion of Honeyman et al. that is set forth above, the teachings of Honeyman et al. are nearly identical to the teachings of Wilton et al., in short, both references teach the *formation of secondary structures* for purposes of detecting genes on a gel that are otherwise undetectable; neither reference teaches, suggests, or even contemplates a primer that is designed to *disrupt secondary structures* in order to expose a site of interest that is located therein.

In the "Claim Construction" discussion set forth on page 2 of the FOA, the Examiner continues to discredit the limitations of the claimed invention by characterizing the "functional" limitations as being on the target molecule, rather than on the claimed primers. The Examiner's approach with respect to the examination of the claimed invention is evident by the last sentence of the "Claim Construction" discussion where the Examiner states that "the claimed primer is anticipated by *any* prior art primer for which a target sequence exists such that the functional limitations and intended uses in the claims are fulfilled." (Emphasis added.) By interpreting the claimed primer with respect to the target, rather than by its own claim limitations, the Examiner attempts to justify the improper approach discussed above, whereby any primer taught in any biotechnology reference may be used to "read on" the claimed invention.

Further, applicants submit that the Examiner's act of conferring limitations to the claims by way of the target, rather than by the characteristics of the claimed primer, turns a blind eye to the mandates set forth in the Decision on Appeal, which is that *all claim limitations* must be considered by the Examiner. The end result of the Examiner's misapplication and

mischaracterization of the BPAI's guidance in the Decision on Appeal is that the Examiner justifies the reopening of the prosecution of this case with a reference, such as Honeyman et al., which essentially provides an identical teaching to that in the Wilton et al. reference.

With reference to the Decision on Appeal, as noted above, the BPAI reversed the Examiner because the Examiner was ignoring the blocking sequence (b) of the claimed primers and probes as being a functional limitation that was accorded no patentable weight. In the FOA, the Examiner now takes the position that the "functional limitations" of the claims (*i.e.*, the blocking sequence) confers no structure to the claimed primer and is merely a function of the target sequence to which the claimed primer is intended to copy or amplify (FOA, p. 2, item 2). The Examiner's "functional" interpretation of the blocking sequence in the FOA is no different from the Examiner's prior act of completely ignoring the blocking sequence. The blocking sequence is an actual part of the claimed primers and probes; it consists of a sequence that is designed to be substantially complementary to a segment of a secondary structure forming region such that it disrupts formation of the secondary structure to expose a site of interest for detection and amplification. Interpreting the blocking sequence any other way is not proper and should not be condoned.

The foregoing discussion explains the clear errors in fact and law with the anticipation rejection of the claimed invention over Honeyman et al. Because the conventional and snapback SSCP primers of Honeyman et al. do not expressly or inherently anticipate the claimed primers and probes for at least the reasons set forth above, applicants respectfully request that this Honorable Board reverse the rejection of 1-5, 9-14, 26, and 32 as anticipated by Honeyman et al.

**B. CLAIMS 6-8, 15, AND 16 ARE NOT OBVIOUS OVER
HONEYMAN ET AL. IN VIEW OF LAIBINIS ET AL.**

Applicants appeal the rejection of claims 6-8, 15, and 16 as obvious under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of Laibinis et al. Claims 6-8, 15, and 16 depend from claim 1. For purposes of this appeal, claims 6-8, 15, and 16 stand together with claim 1.

The Examiner cites Laibinis et al. for the non-hybridizing spacer and arresting linker of claim 6-8, 15, and 16. Claims 6-8, 15, and 16 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 6-8, 15, and 16 are not rendered obvious by Honeyman et al. in view of Laibinis et al. In view of the foregoing, applicants respectfully request that this Honorable Board reverse this rejection.

C. CLAIMS 10 AND 11 ARE NOT OBVIOUS OVER

HONEYMAN ET AL. IN VIEW OF SWITZER ET AL.

Applicants appeal the rejection of claims 10 and 11 as obvious under 35 U.S.C. § 103(a) as obvious over Honeyman et al. in view of Switzer et al. Claims 10 and 11 depend from claim 1. For purposes of the appeal, claims 10 and 11 stand together with claim 1.

The Examiner cites Switzer et al. for the non-natural nucleotide spacers of claims 10 and 11. Claims 10 and 11 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 10 and 11 are not rendered obvious by Honeyman et al. in view of Switzer et al. In view of the foregoing, applicants respectfully request that this Honorable Board reverse this rejection.

D. CLAIMS 17, 18 AND 33, AND 34 ARE NOT OBVIOUS OVER

HONEYMAN ET AL. IN VIEW OF BEATTIE ET AL.

Applicants appeal the rejection of claims 17, 18, 33, and 34 as obvious over 35 U.S.C. § 103(a) by Honeyman et al. in view of Beattie et al. Claims 17 and 18 depend from claim 1 and claims 33 and 34 depend from claim 32. For purposes of the appeal, claims 17 and 18 stand together with claim 1 and claims 33 and 34 stand together with claim 32. As set forth above, claims 1 and 32 stand together.

The Examiner cites Beattie et al. for the detectable label of claims 17, 18, 33, and 34. Claims 17 and 18 depend from claim 1 and claims 33 and 34 depend from claim 32. Because Honeyman et al. do not teach or suggest claims 1 and 32 for the reasons set forth above, it follows that claims 17, 18, 33, and 34 are not rendered obvious by Honeyman et al. in view of Beattie et al. In view of the foregoing, applicants respectfully request that this Honorable Board reverse this rejection.

E. CLAIMS 27-31 ARE NOT OBVIOUS OVER

HONEYMAN ET AL. IN VIEW OF THE STRATAGENE CATALOGUE

Applicants appeal the rejection of claims 27-31 as obvious under U.S.C. § 103(a) by Honeyman et al. in view of the Stratagene Catalogue. Claims 27-31 depend from claim 1. For purposes of the appeal, claims 27-31 stand together with claim 1.

The Examiner cites the Stratagene Catalog for the kit of claims 27-31. Claims 27-31 depend from claim 1. Because Honeyman et al. do not teach or suggest claim 1 for the reasons set forth above, it follows that claims 27-31 are not rendered obvious by Honeyman et al. in view

of the Stratagene Catalog. In view of the foregoing, applicants respectfully request that this Honorable Board reverse this rejection.

F. CLAIMS 1 AND 32 ARE NOT OBVIOUS OVER HOGAN ET AL.

Applicants appeal the rejection of claims 1 and 32 as obvious under 35 U.S.C. § 103(a) over Hogan et al. For purposes of the appeal of this rejection, claims 1 and 32 stand together.

The Court of Appeals for the Federal Circuit has explained that the rationale to support a conclusion that a claim would have been obvious is that “a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.” USPTO Examination Guidelines, 72 Fed. Reg. 195 (2007) quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006).

At page 8 of the FOA, the Examiner states that Hogan et al. teach a combination of a primer sequence and a helper sequence in which the helper sequence blocks intramolecular secondary hairpin target formation to facilitate PCR of target regions. Applicants submit that the Examiner's interpretation of Hogan et al. is not correct. The following discussion will explain why.

1. THE TEACHINGS OF HOGAN ET AL.

Hogan et al., which is discussed in the Background of the instant application, teach that secondary and tertiary structures that are not lost under conditions normally used for nucleic acid hybridization (*e.g.*, elevated temperature, salt, and accelerators) may be disrupted through the use of helper oligonucleotides that bind to a portion of RNA or DNA other than that being targeted by the probe. According to Hogan et al., the helper oligonucleotides *impose new secondary or tertiary structures on the targeted region of the single stranded nucleic acid thereby accelerating the hybridization process* (col. 4, ll. 18-43). At col. 6, ll. 24-28, Hogan et al. explain that the effect of helper oligonucleotides on the kinetics of hybridization is the result of *reordering of the secondary and tertiary structure of the single stranded targeted nucleic acid*. At col. 7, ll. 19-27, Hogan et al. teach that in some cases, the helper oligonucleotide may be selected to bind to a region in the target nucleic acid that is immediately adjacent to the probe binding sequence. In such a case, limited overlap between the region binding the probe and the region binding to the helper can be tolerated, but is usually not desirable. In other cases, the helper may exhibit the desired effect even though it binds to a region removed from the region binding the probe. At

col. 7, ll. 50-65, Hogan et al. teach that the helper oligonucleotide is typically used in excess compared to the target and/or the probe. When the probe is used in excess compared to the target, the helper oligonucleotide is typically used in a molar concentration of at least 5 times to more than 100 times that of the probe. When the target is in excess compared to the probe, the helper oligonucleotide is typically used in a molar concentration of at least 10 times to more than 100 times that of the probe.

Example 1 of Hogan et al. describes the use of two helper oligonucleotides to assist in the hybridization of the 16S rRNA of *Salmonella*, which exhibits a closed intrastrand helical structure in the 430-500 region of the 16S ribosome (Figure 2). Helper A was designed to bind in about the 430-450 region and Helper B was designed to bind in the 480-510 region; both Helpers were used in a molar concentration of 100 times that of the probe. Example 2 of Hogan et al. describes the use of nine helper oligonucleotides to assist in the hybridization of 16S rRNA of *Neisseria*, which exhibits a closed intrastrand helical structure in the 130-150, 460-480, and 980-1010 regions (Figure 3). Helper C was designed to bind to the rRNA in the region immediately adjacent to the probe at about 110, Helpers D and E were designed to bind in regions of the rRNA remote from that bound by the probe at about 190 and 250, respectively; Helper F was designed to bind to the 450 region; Helper G was designed to bind to the 510 region; Helper H was designed to bind to the 35 region; Helper I was designed to bind to the 960 region; Helper J was designed to bind to the 1020 region; and Helper K was designed to bind to the 1210 region. Example 3 describes the use of two helper oligonucleotides to assist in the hybridization of region 450 of the 16S ribosomal RNA of *E. coli*. The assays were run with a molar ratio of helper to probe of 250:1.

2. CLAIMS 1 AND 32

As noted above, in the Office Action under reply, the Examiner states that Hogan et al. teach a combination of a primer sequence and a helper sequence in which the helper sequence blocks intramolecular secondary hairpin target formation to facilitate PCR of target regions. On this characterization of Hogan et al., applicants note that Hogan et al. never references a “primer” and only uses the term “probe.” Further, Hogan et al. do not teach or suggest the use of the probe described therein for PCR, presumably because PCR was in its infancy at the November 24, 1987, filing date of Hogan et al. Lastly, as discussed above, the method of Hogan et al. *enhances* hybridization, not by breaking residual secondary or tertiary structures that remain

after normal hybridization conditions, but rather, by using the helper sequences to *reorder* the secondary or tertiary structures on the targeted region so that the *rate of hybridization* of the probe is enhanced (*see*, col. 4, ll. 29-43; col. 6, ll. 25-30).

At page 8 of the Office Action, the Examiner admits that Hogan et al. do not teach the “primer” and helper in a single sequence, but asserts that one of skill in the art would have been motivated to combine the “primer” and the helper of Hogan et al. into a single sequence because primer design is routine and obvious to the skilled artisan. The Examiner adds that there are two ways to combine the sequences of Hogan et al., with a linking sequence or directly as a single contiguous sequence and that a skilled artisan would have been motivated to combine the two sequences because a single sequence results in a lower cost assay, which is less labor intensive and more practical.

Applicants disagree with the Examiner’s obviousness analysis. Based solely on a reading of Hogan et al., there is no teaching or suggestion therein that would lead one of ordinary skill in the art to be motivated to prepare a single sequence from the probe and excess helpers disclosed therein. As discussed above, Hogan et al. teach the use of multiple helper sequences that are in at least 5x molar excess of the probe sequence when the probe is used in excess to the target and at least 10x molar excess of the probe when the target is in excess to the probe (col. 7, ll. 50-65). The Examiner’s obviousness analysis does not address the fact that the Hogan et al. helper sequences are in molar excess and consequently, provides no evidence on how one of skill in the art would be able to combine the molar excess helper sequences into the single probe sequence of Hogan et al.

Notwithstanding the foregoing, even if the ordinary artisan were to attempt to prepare a single probe that incorporates the helper sequences in the 5x to 100x molar excess taught by Hogan et al., the resulting probe would be so large that the ordinary artisan would not have a reasonable expectation that the probe would be successful at hybridizing to the target. The large size of the resulting single-stranded probe would likely result in the probe folding in upon itself. Further, the presence of the molar excess helpers in the single-stranded probe would likely result in the crowding of the probe sequence rendering it ineffective for hybridization. Such a probe would not fulfill the purpose of Hogan et al., which is the enhancement of nucleic acid hybridization through the reordering of the secondary and tertiary structures on the target sequence (not on the probe) thus enhancing the rate of binding of the probe to the target region.

Because the teachings of Hogan et al. do not render the claimed primers and probes obvious for the reasons set forth above, applicants respectfully request that this Honorable Board withdraw this rejection.

VIII. CONCLUSION

The foregoing discussion identifies the clear errors in fact and law in the rejections of the claimed invention. Because the claimed invention is not anticipated by or rendered obvious by the cited references, applicants respectfully request that this Honorable Board withdraw the rejections from the outstanding Office Action and allow the subject application to pass to issue.

Respectfully submitted,

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IX. CLAIMS APPENDIX

1. **(Previously presented)** A dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

2. **(Original)** The primer of claim 1, wherein the site of interest is a nucleic acid sequence.

3. **(Original)** The primer of claim 2, wherein the site of interest is a single nucleotide polymorphism.

4. **(Original)** The primer of claim 1, wherein the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence.

5. **(Original)** The primer of claim 1, further including a nonhybridizing spacer between the primer sequence and the blocking sequence.

6. **(Original)** The primer of claim 5, wherein the spacer is non-nucleotidic.

7. **(Original)** The primer of claim 6, wherein the spacer is comprised of a synthetic hydrophilic oligomer.

8. **(Original)** The primer of claim 7, wherein the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide.
9. **(Original)** The primer of claim 5, wherein the spacer is nucleotidic.
10. **(Original)** The primer of claim 9, wherein the spacer is comprised of a sequence of non-natural nucleotides.
11. **(Original)** The primer of claim 10, wherein the non-natural nucleotides are selected from iso-guanine and iso-cytosine.
12. **(Previously presented)** The primer of claim 9, wherein the spacer is an oligomeric segment of a recurring single nucleotide.
13. **(Currently amended)** The primer of claim 9, wherein the ~~probe~~ primer sequence and the spacer are separated from each other by a means for halting transcription therebetween.
14. **(Original)** The primer of claim 13, wherein the means for halting transcription is an arresting linker.
15. **(Original)** The primer of claim 14, wherein the arresting linker comprises at least one modified nucleoside.
16. **(Original)** The primer of claim 15, wherein the modified nucleoside is an N⁴-modified pyrimidine.
17. **(Original)** The primer of claim 1, further comprising a detectable label.

18. **(Original)** The primer of claim 17, wherein the detectable label is selected from the group consisting of fluorescers, chemilumescers, dyes, biotin, haptens, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, enzyme subunits, metal ions, electron-dense reagents, and radioactive isotopes.

26. **(Original)** An amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence.

27. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, nucleotides appropriate to amplification of an oligonucleotide sequence, and an agent for polymerization of the nucleotides.

28. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH probe such that the target nucleotide sequence is identified by the color-coding of said detecting means.

29. **(Original)** The kit of claim 28, wherein the detecting means is a multiplex detecting means.

30. **(Original)** The kit of claim 29, wherein the multiplex detecting means comprises a detectable solid substrate.

31. **(Original)** The kit of claim 30, wherein the detectable solid substrate is a detectable microsphere.

32. **(Previously presented)** A hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

33. **(Original)** The hybridization probe of claim 32, further comprising a detectable label.

34. **(Original)** The hybridization probe of claim 33, wherein the detectable label is selected from the group consisting of chemiluminescent labels, fluorescent labels, radioactive labels, multimeric DNA labels, dyes, enzymes, enzyme modulators, detectable solid substrates, and metal ions.

X. EVIDENCE APPENDIX

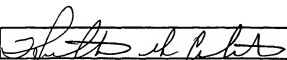
Exhibit A: Signed Honeyman et al. PTO-1449 dated August 9, 2006.
Exhibit B: Signed Hogan et al. PTO-1449 dated August 9, 2006.

EXHIBIT A

Substitute for form 1449A/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Application Number	Unassigned
				Filing Date	Concurrently herewith
				First Named Inventor	John J. QUINN et al.
				Art Unit	Unassigned 1637
				Examiner Name	Unassigned CACHMITH
Sheet	1	of	1	Attorney Docket Number	1300-0007

U.S. PATENT DOCUMENTS							
Examiner Initials*	Cite No.	Document No.	Issue Date or Publication Date	Name of Patentee or Applicant of Cited Document	Class	Subclass	Filing Date if Appropriate
<i>Hae</i>	AA	5,030,557	7/9/91	Hogan et al.			
	AB	5,124,246	6/23/92	Urdea et al.			
	AC	5,200,314	4/6/93	Urdea			
	AD	5,256,535	10/26/93	Ylikoski et al.			
	AE	5,525,494	6/11/96	Newton			
	AF	5,622,822	4/22/97	Ekeze et al.			
	AG	5,624,802	4/29/97	Urdea			
	AH	5,648,482	7/15/97	Meyer			
	AI	5,710,264	1/20/98	Urdea et al.			
	AJ	5,736,327	4/7/98	Collins			
	AK	5,747,248	5/5/98	Collins			
	AL	5,800,994	9/1/98	Martinelli et al.			
	AM	5,827,648	10/27/98	Eastman et al.			
	AN	5,849,481	12/15/98	Urdea et al.			
	AO	5,981,180	1/9/99	Chandler et al.			
	AP	6,046,807	4/4/00	Chandler			
	AQ	6,139,800	10/31/00	Chandler			
	AR	6,187,538	2/13/01	Eastman et al.			
	AS	6,261,773	7/17/01	Segawa et al.			
	AT	6,268,222	7/31/01	Chandler et al.			
	AU	6,287,778	9/11/01	Huang et al.			
	AV	6,316,202	11/13/01	Barnes et al.			
	AW	6,322,980	11/27/01	Singh			
	AX	2001/0009760	7/26/01	Horn et al.			
	AY	2001/0026918	10/4/01	Collins et al.			
	AZ	2002/0006643	1/17/02	Kavyem et al.			
<i>Hae</i>	BA	2002/0031764	3/14/02	Koch			

OTHER DOCUMENTS — NONPATENT LITERATURE DOCUMENTS							
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), Title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.					T
<i>Hae</i>	BB	MIR et al. (2000), "Sequence Variation in Genes and Genomic DNA: Methods for Large-Scale Analysis," <i>Annu. Rev. Genomics. Hum. Genet.</i> 1:329-360.					
<i>Hae</i>	BC	WHITCOMBE et al. (1999), "Detection of PCR Products Using Self-Probing Amplicons and Fluorescence," <i>Nature Biotechnology</i> 17:804-807					

Examiner Signature		Date Considered	07/27/06
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

EXHIBIT B

Supplemental form for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Complete if Known Application Number 10/667,191 Filing Date September 15, 2003 First Named Inventor John J. QUINN et al. Art Unit 1637 Examiner Name Unassigned / ALAMITA Attorney Docket Number 1300-0007	
SHEET 1 of 1 AUG 06 2003 OPIE & PATENT & TRADEMARK OFFICE			

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document No.	Issue Date or Publication Date	Name of Patentee or Applicant of Cited Document	Class	Subclass	Filing Date if Appropriate
Hoe	BD	5,310,678	5/10/94	Bingham et al.			
	BE	5,573,906	11/12/96	Bannwarth et al.			
	BF	6,136,568	10/24/00	Hiatt et al.			
Hoe	BG	2002/028455	3/7/02	Laibinis et al.			

FOREIGN PATENT DOCUMENT

Examiner Initials*	Cite No.	Foreign Patent Document No.	Publication Date	Country	Class	Subclass	T
Hoe	BH	WO 00/71243 A1	11/30/00	PCT			

OTHER DOCUMENTS — NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), Title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
Hoe	BI	HONEYMAN et al. (1999), "Development of a Snapback Method of Single-Strand Conformation Polymorphism Analysis for Genotyping Golden Retrievers for the X-Linked Muscular Dystrophy Allele," <i>AJVR</i> 60(6):734-737.	
Hoe	BJ	LIN et al. (1989), "Synthesis and Duplex Stability of Oligonucleotides Containing Cytosine-Thymine Analogues," <i>Nucleic Acids Research</i> 17(24):10373-10383.	
Hoe	BK	WILTON et al. (1998), "Snapback SSCP Analysis: Engineered Conformation Changes for the Rapid Typing of Known Mutations," <i>Human Mutation</i> 11:252-258.	

Examiner Signature		Date Considered	07/27/06
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

XI. RELATED PROCEEDINGS APPENDIX

The prior Decision on Appeal for the instant case is attached to this paper.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,191	09/15/2003	Minxue Zheng	1300-0007	9085
28524 7590 02/23/2010 SIEMENS CORPORATION INTELLECTUAL PROPERTY DEPARTMENT 170 WOOD AVENUE SOUTH ISELIN, NJ 08830			EXAMINER CALAMITA, HEATHER	
			ART UNIT 1637	PAPER NUMBER
			MAIL DATE 02/23/2010	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MINXUE ZHENG, JOHN J. QUINN,
and BRIAN D. WARNER

Appeal 2009-007969
Application 10/667,191
Technology Center 1600

Decided: February 23, 2010

Before DONALD E. ADAMS, ERIC GRIMES, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the rejections of claims 1-18 and 26-35. The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b) and 134. The rejections are reversed.

STATEMENT OF THE CASE

According to the Specification, intramolecular secondary structure may form in a single-stranded nucleic acid molecule when complementary nucleotide sequences within the molecule hybridize together (Spec. 1-2: ¶¶ 3-4). Such secondary structures can mask or conceal allelic variations associated with the regions of secondary structure (*id.* at 3: ¶ 8). As a result, a primer designed to detect a nucleotide variation may be unable to hybridize with the variation, producing no signal even when the variation is present (*id.* at 1-2: ¶¶ 3-5). To address this problem, the Specification describes a dual-purpose primer with a primer sequence and a blocking sequence. In certain embodiments, the primer is utilized to amplify a target sequence of interest (*id.* at 3: ¶ 9; 5: ¶ 19). After amplification, the blocking sequence hybridizes to its complement in the amplified sequence of interest, blocking unwanted secondary structure and revealing the masked allelic variation (*id.*).

Claims 1-18 and 26-35 are pending and stand rejected by the Examiner as follows:

1. Claims 1-18 and 26-35 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Ans. 3);
2. Claims 1-5, 9, 12-14, and 26 under 35 U.S.C. § 102(b) as anticipated by Wilton (Wilton et al., Snapback SSCP Analysis: Engineered Conformation Changes for the Rapid typing of Known Mutations, HUMAN MUTATION, vol. 11, pp. 252-258 (1998)) (Ans. 5);
3. Claims 1, 2, and 4-7 under 35 U.S.C. § 102(b) as anticipated by Bannwarth (Bannwarth et al., US 5,573,906, Nov. 12, 1996) (Ans. 7);

4. Claims 1 and 5-8 under 35 U.S.C. § 102(b) as anticipated by Laibinis (Laibinis et al., US 2002/0028455 A1, Mar. 7, 2002) (Ans. 9);

5. Claims 1, 17, and 18 under 35 U.S.C. § 102(b) as anticipated by Beattie (Beattie et al., US 6,268,147 B1, Jul. 31, 2001) (Ans. 10);

6. Claims 27-32 under 35 U.S.C. § 103(a) as obvious in view of Wilton and the Stratagene Catalog (Stratagene catalog, p. 39 (1988)) (Ans. 11).

7. Claim 28 under 35 U.S.C. § 103(a) as obvious in view of Bannwarth and the Stratagene catalog (Ans. 13).

8. Claims 28-34 under 35 U.S.C. § 103(a) as obvious in view of Beattie and the Stratagene catalog (Ans. 14).

9. Claims 10, 11, 15, and 16 under 35 U.S.C. § 103(a) as obvious in view of Wilton and Fisher (Fisher, US 6,054,568, Apr. 25, 2000) (Ans. 16).

Claim 1 is representative and reads as follows:

1. A dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

CLAIM INTERPRETATION

Statement of the Issue

Did the Examiner properly interpret the scope of claim 1 by ignoring its functional limitations?

Principles of Law

A patent applicant is free to recite features of an apparatus either structurally or functionally. See *In re Swinehart*, 439 F.2d 210, 212, (CCPA 1971) (“[T]here is nothing intrinsically wrong with... [defining something by what it does rather than what it is] in drafting patent claims.”). Yet, choosing to define an element functionally, i.e., by what it does, carries with it a risk. As our predecessor court stated in *Swinehart*, 439 F.2d at 213: where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997).

Analysis

The functional limitations

Claim 1 is to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule. The dual-purpose primer comprises two key elements, recited in functional, rather than structural, terms. We address each below:

- “(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region”

The dual-primer is recited to have a “primer sequence.” The primer sequence is not described as having a specific structure or sequence. Instead, the primer is recited to have “a primer sequence complementary to a segment of the target nucleotide sequence.” The term “primer” is defined in the Specification as “an oligonucleotide . . . which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product that is complementary to a nucleic acid strand is induced” (Spec. 8: ¶ 31). From its definition in the Specification, it would be understood that nucleotide sequence complementarity is necessary for the primer to serve as an initiator of nucleic acid synthesis. Thus, limitation (a) requires the “primer sequence” to be capable of acting as an initiator of nucleic acid synthesis. Any nucleotide sequence which is capable of this function would meet the claimed limitation; it is not limited to a particular sequence of nucleotides or size.

- *“(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.”*

Secondly, the dual-purpose primer is recited to have a “blocking sequence.” The “blocking sequence” is not required by the claim to have a specific sequence of nucleotides. Rather, it is defined by the claim as complementary to a “secondary structure forming region” and to have the function of disrupting “formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of

interest.” Therefore, to meet the “blocking sequence” limitation, a dual-purpose primer must comprise a portion which is complementary to a region that is capable of forming secondary structure *and* which disrupts the secondary structure when hybridized to the region.

The Examiner did not give weight to the “blocking sequence” limitation because it was a “functional limitation,” arguing that “such functional limitations and recitations of intended use confer no structural limitations to the claimed primer” (Ans. 3).

The Examiner erred in interpreting the claim. “A patent applicant is free to recite features . . . either structurally or functionally.” *In re Schreiber*, 128 F.3d at 1478. A claim element which is recited in terms of function, instead of structure, still limits the claim. (*Microprocessor Enhancement Corp. v. Texas Instruments Inc.*, 520 F.3d 1367, 1375 (Fed. Cir. 2008) (“Functional language may also be employed to limit the claims without using the mean-plus-function format.”)) The patent statute specifically provides for a class of functional limitations written in “means-plus-function” format, where the claimed element is recited “as a means or step for performing a specified function without the recital of structure, material or actions.” 35 U.S.C. § 112, sixth paragraph. Thus, claiming “blocking sequence” in terms of its function, rather than structure, was not a proper basis to disregard it as a limitation of the claim.

The “dual-purpose primer”

According to the Specification, the primer is characterized as a “dual-purpose” because it has both a “primer sequence,” which is effective to amplify a target nucleic acid, and a “blocking sequence,” which disrupts

secondary structure in a single-stranded form of the target nucleic acid (Spec. 3: ¶ 8). These two sequences correspond to elements (a) and (b), respectively, of claim 1.

The “primer” portion (element “(a)”) of the dual-purpose primer “is relatively short, generally on the order of 10 to 30 bases in length” and the blocking sequence portion (element “(b)”) “can also be relatively short,” for example, 8 to 12 bases in length (*id.* at 14: ¶ 57). Dual-purpose primers from 55 to 59 nucleotides were utilized in Example 2 (*id.* at 26-27: ¶ 98; SEQ ID NOS: 16-23). However, we do not limit the dual-purpose primer to these sizes; rather, any sized nucleic acid which can perform the primer and blocking sequence functions would meet the limitations of the claim.

WRITTEN DESCRIPTION REJECTION

Claims 1-18 and 26-35 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Ans. 3).

Statement of the Issue

Did the Examiner err in rejecting claim 1 for failing to comply with the written description requirement?

Principles of Law

A fully described genus must allow one skilled in the art to “visualize or recognize the identity of the members of the genus” and to “distinguish the claimed genus from others.” *University of California v. Eli Lilly & Co.* (“*Lilly*”), 119 F.3d 1559, 1568 (Fed. Cir. 1997).

“[A]pplicants have some flexibility in the ‘mode selected for compliance’ with the written description requirement,” but a specification

must “set forth enough detail to allow a person of ordinary skill in the art . . . to recognize that the inventor invented what is claimed.” *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 928 (Fed. Cir. 2004).

[T]he written description requirement can be met by “show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.”

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) (emphasis omitted, alterations in original).

“[W]hat is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). “[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).” *Capon*, 418 F.3d at 1359.

Analysis

Citing *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991), and *University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997), the Examiner determined that the Specification did not fully describe the genus of the claimed nucleic acids because the “skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids” (Ans. 4). The

Examiner found that the claims encompassed “any polynucleotide for which a target sequence exists *or could be synthesized*,” but determined that the Specification did not describe a representative number within the scope of the claim (*id.* at 5).

Since no specific polynucleotide sequence or no specific template sequence is recited, Applicants have not described the sequence information required to define the genus of all primers that would provide the requisite functional limitations required by the claims.

Therefore, . . . Applicants have not adequately defined the genus in terms of the structure required to perform the function and have not adequately described the enormous number of potential primers falling within the genus claimed.

(*Id.*)

In the *Fiers*, *Amgen*, and *Eli Lilly* cases, the inventor asserted to have invented a nucleic acid molecule coding for a specific polypeptide. Because the novelty of the sequence, itself, was at issue, the court imposed the requirement under section 112, first paragraph, that the Specification describe the complete nucleotide sequence of the claimed nucleic acid, along with a representative number of examples within the scope of the claim. However, this was not an inflexible requirement for all nucleic acid claims. As discussed in *Capon*, support for a generic claim “to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Capon*, 418 F.3d at 1359.

In this case, the inventors do not assert to have invented a specific nucleotide sequence. Rather, the invention is characterized as a conventional primer sequence coupled to a blocking sequence, where the

latter unmasks allelic variations that are otherwise concealed by secondary structure when the dual-purpose primer is used in amplification reactions (Spec. 4: ¶ 13, 5: ¶ 19, 18: ¶ 69; & 19: ¶ 72). As indicated in the Specification, selection of suitable sequences with these functions for any given target sequence would have been routine (*id.*). It was not appropriate to require a written description of a representative nucleic acid as in the line of cases represented by the *Lilly* case because the invention is not a specific nucleic acid sequence, per se, but a generic dual-purpose primer with priming and blocking functions to enable detection of masked allelic variations.

There is no rigid test for compliance with the written description requirement. Rather, the Specification must set forth sufficient detail to establish that the inventors invented what is claimed. Written description of a complete invention can be shown by sufficiently detailed and identifying characteristics. *Enzo*, 323 F.3d at 964. The written description must be viewed in the eyes of the ordinary skilled worker and the knowledge accorded to him. *See Capon*, 418 F.3d at 1359. To this end, the Specification established that the existing knowledge in the art was substantial: primer design, hybridization, and secondary structure were well characterized at the time of the invention (Spec. 1-2; 2: ¶ 6; 9: ¶ 36). Using this knowledge, persons of ordinary skill in the art could routinely select dual-purpose primers with priming and blocking functions. The Specification generically described the dual-purpose primer (*id.* at 5: ¶ 19; 13: ¶ 53; 14: ¶ 57; 17: ¶ 67; 18: ¶¶ 68-69). Based on the generic description coupled with the established maturity of the field, persons of ordinary skill

in the art would have recognized that the description of the invention was complete.

ANTICIPATION REJECTIONS

Claims 1-5, 9, 12-14, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Wilton (Ans. 5).

Claims 1, 2, and 4-7 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bannwarth (Ans. 7).

Claims 1 and 5-8 stand rejected under 35 U.S.C. § 102(b) as anticipated by Laibinis (Ans. 9).

Claims 1, 17, and 18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Beattie (Ans. 10).

Statement of the Issue

Do the Wilton, Bannwarth, Laibinis, and Beattie publications describe the claimed dual purpose primer with primer and blocking sequences?

Principles of Law

“To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently.”
In re Schreiber, 128 F.3d at 1477.

The PTO does not have the ability “to manufacture products or to obtain and compare prior art products.” *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Thus, once “the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

Analysis

The Examiner had the burden of establishing a sound basis to believe that claimed dual-purpose primer was described in the prior art. This burden was not met. Although the Examiner provided evidence that the prior art nucleic acids of Wilton, Bannwarth, Laibinis, and Beattie, each had a sequence capable of performing the primer function of element (a), the Examiner improperly gave element (b) no weight. The Examiner asserted that the “blocking sequence” imparted no limitation to the claim and did not compare it to the prior art (Ans. 6, 8, 9, and 11). As discussed above, a claim element which is recited in terms of function, instead of structure, still limits the claim. The Examiner therefore erred in interpreting claim 1 by disregarding an explicit limitation of the claim. As the Examiner did not provide a factual basis upon which to believe that the primers of Wilton, Bannwarth, Laibinis, and Beattie comprise a “blocking sequence” capable of disrupting secondary structure, we are compelled to reverse all the rejections for anticipation.

OBVIOUSNESS REJECTIONS

Claims 27-32 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Wilton and the Stratagene Catalog (Ans. 11).

Claim 28 stands rejected under 35 U.S.C. § 103(a) as obvious in view of Bannwarth and the Stratagene Catalog (Ans. 13).

Claims 28-34 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Beattie and the Stratagene Catalog (Ans. 14).

Claims 10, 11, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Wilton and Fisher (Ans. 16).

All the claims rejected under § 103(a) require a dual-primer with (a) a primer sequence and (b) a blocking sequence. As the Examiner did not establish that the cited prior art publications described the claimed blocking sequence, we are compelled to reverse the rejections.

REVERSED

alw

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